PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference LTT-98	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/JP2004/015026	International filing date *(day/month/year)* 12 October 2004 (12.10.2004)	Priority date *(day/month/year)* 24 December 2003 (24.12.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant LTT BIO-PHARMA CO., LTD.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 24 July 2006 (24.07.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yoshiko Kuwahara e-mail: pt07@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	
Applicant's or agent's file reference **LTT-98**	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/015026	**12.10.2004**	**24.12.2003**

International Patent Classification (IPC) or both national classification and IPC

Applicant
LTT BIO-PHARMA CO., LTD.

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP Facsimile No.	Authorized officer Telephone No.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2004/015026

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2004/015026

Box No. V **Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-26	YES
	Claims		NO
Inventive step (IS)	Claims	1	YES
	Claims	2-26	NO
Industrial applicability (IA)	Claims	1-26	YES
	Claims		NO

2. Citations and explanations:

The following documents are listed in the international search report.

Document 1/WO 2002/051390 A2
Document 2/JP 2002-504425 A
Document 3/Shin Yakuzaigaku Soron (Kaitei Dai 3 Han), 10 April 1987, p. 65-66
Document 4/JP 5-507685 A
Document 5/JP 2002-544177 A
Document 6/Nippon Yauzai Gakkai Dai 17 Nenkai Koen Shoshishu, 5 March 2002, p. 88
Document 7/JP 2003-292420A
Document 8/JP 8-217691 A

(1) Documents 1-8/Inventive step of nanoparticles containing a fat-soluble drug wherein a monovalent to trivalent basic salt acts on secondary nanoparticles

As described in documents 1 and 2, nanoparticles comprising lipids such as fatty acids and the like that contain drugs are widely known to persons skilled in the art (document 1, page 1, line 9 to page 4, line 2; document 2, Claims 1 and 6, Par. Nos. 0013 to 0014 and 0024). Furthermore, this authority finds that it is obvious to persons skilled in the art that amphiphilic substances such as fatty acids and the like form micelles in water (document 3, page 66, Table 2.7; document 4, page 3, lower right column) and that it is difficult to control the sustained release of a drug with lipid nanoparticles containing a drug (document 5, Par. Nos. 0001 to 0002).

On the other hand, document 6 (entire document) describes a method for forming calcium carbonate crystals on the surface of a micelle by adding calcium chloride (a divalent or trivalent metal salt) and sodium carbonate (a monovalent to trivalent basic salt) to nanomicelles of retinoic acid as a method of sustained release of retinoic acid.

Therefore, this authority finds that it is obvious to persons skilled in the art to prepare nanoparticles containing a drug and having calcium carbonate on the surface thereof based on the descriptions in documents 3-6 by causing calcium chloride and sodium carbonate to act on nanoparticles comprising lipids such as fatty acids and the like that contain a drug in order to obtain lipid nanoparticles wherein the sustained release of the drug is controlled.

With respect to the effect that the nanoparticles of the inventions of this application have a high level of absorption into the skin, document 7 states that nano-sized particles such as nanocapsules and the like penetrate the skin and can transport active ingredients into the skin.

(Continued in supplemental box)

Box No. VIII **Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1-26 concern nanoparticles (C) obtained by causing a divalent or trivalent metal salt (B1), or both (B1) and a monovalent to trivalent basic salt (B2) to act on primary nanoparticles (A) containing a lipid-soluble drug.

However, the above claims contain no description whatsoever concerning the structure of (C), and the mode of action of (B1) and (B2) on (A) although clearly many types of particles are included therein, this authority finds that upon looking at the specification, only nanoparticles (C), wherein nanoparticles (A) are coated with the reaction product of salts (B1) and (B2), is described in Example 6, but there is no other location that describes the structure of nanoparticles (C), and the mode of action of salts (B1) and (B2) on nanoparticles (A).

Moreover, although claim 3 and subsequent claims are written to limit nanoparticles (A) to those produced by the action of a lipid-soluble drug, a medium or long chain organic compound with anionic residues, and a surfactant, the claims contain no other description of the structure of nanoparticles (A) although clearly many types of particles are included therein. This authority finds that the examples in the specification only present nanoparticles (A) wherein a lipid-soluble drug is incorporated into micelles comprising a medium or long chain organic compound with anionic residues, and does not present any other description specifying the structure of nanoparticles (A) and the like.

This being the case, the details of the inventions are unclear from the descriptions of these claims and the description in the specification is insufficiently clear for persons skilled in the art to implement the invention. As a result, this authority finds that the inventions of these claims are not sufficiently supported by the specification (PCT Articles 5 and 6).

In addition, because the specification and the description of the claims fails to satisfy the aforementioned requirement, it should be noted that this written opinion is based only on a reasonable scope for the inventions of these claims in accordance with the explanation in the specification.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: Box V.

Therefore, this matter is obvious to persons skilled in the art (document 7, Par. Nos. 0002 to 0004).

In addition, with respect to the surfactant, this authority finds that it is obvious to persons skilled in the art to add a surfactant to stabilize lipid nanoparticles (document 1, page 9, lines 13 to 18).

Furthermore, with respect to the drug, this authority finds that, as described in document 1, lipid nanoparticles provide excellent incorporation of drugs that are poorly soluble in water, and therefore it is obvious to persons skilled in the art to use a lipid-soluble drug as the drug and to use a water-soluble drug that has been lipid-solubilized by a publicly known method (document 1, page 2, lines 8 to 15; document 8, Par. No. 0009).